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Cortisol excess in patients with primary aldosteronism impacts on left ventricular hypertrophy

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Précis: Left ventricular mass in patients with primary aldosteronism improves after medical and surgical treatment and is positively correlated with total glucocorticoid excretion.

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Abstract

Context: Primary aldosteronism (PA) represents the most frequent form of endocrine hypertension. Hyperaldosteronism and hypercortisolism both induce excessive left ventricular hypertrophy (LVH) compared to matched essential hypertensives. In recent studies frequent co-secretion of cortisol and aldosterone has been reported in PA patients.

Objective: Our aim was to investigate the impact of cortisol co-secretion on left ventricular hypertrophy in PA patients. We determined 24-h excretion of mineralocorticoids and glucocorticoids by gas chromatography-mass spectrometry and assessed cardiac remodeling using echocardiography initially and one year after initiation of treatment for PA.

Patients: We included 73 patients from the Munich center of the German Conn's registry; 45 with unilateral aldosterone-producing adenoma and 28 with bilateral adrenal hyperplasia.

Results: At the time of diagnosis, 85% of PA patients showed left ventricular hypertrophy according to left ventricular mass index (LVMI, median 62.4 $g/m^{2.}$). LVMI correlated positively with total glucocorticoid excretion (r^2=0.076, p=0.018) as well as with tetrahydroaldosterone excretion (r^2=0.070, p=0.024). Adrenalectomy led to significantly reduced LVMI in aldosterone-producing adenoma (p<0.001) while mineralocorticoid receptor antagonist therapy in bilateral adrenal hyperplasia patients reduced LVMI to a lesser degree (p=0.024). In multivariate analysis, the decrease in LVMI was positively correlated with total glucocorticoid excretion and systolic 24-hour blood pressure, but not with tetrahydroaldosterone excretion.

Conclusion: Cortisol excess appears to have an additional impact on cardiac remodeling in patients with PA. Treatment of PA by either adrenalectomy or mineralocorticoid receptor antagonist improves LVMI. This effect was most pronounced in patients with high total glucocorticoid excretion.

Introduction

Primary aldosteronism (PA) is the most frequent cause of endocrine hypertension affecting about 5-10 % of patients with elevated blood pressure (1). PA was first described in 1955 by Jerome W. Conn (2) and characterized in its classical form as hypertension, hypokalemia and alkalosis. Patients with bilateral adrenal hyperplasia (BAH), the most common subtype, require lifelong treatment with a mineralocorticoid receptor antagonist (MRA), whereas patients with unilateral aldosterone-producing adenoma (APA) can be cured by adrenalectomy (ADX). Prolonged exposure to elevated aldosterone concentrations causes cardiac and renal damage independently of blood pressure (3). These changes may have adverse impact on clinical outcome.

One of the targets of aldosterone action are cardiomyocytes which express mineralocorticoid receptors (MR) (4). Indeed, MR activation has been shown to induce myocardial damage (3), including diffuse myocardial fibrosis, left ventricular hypertrophy (LVH) and left ventricular dilatation (4). In echocardiographic studies, LVH was more frequent and more progressive in PA patients in comparison to matched essential hypertensives (5). Likewise, a number of studies have highlighted an increased risk of stroke, myocardial infarction (MI) and atrial fibrillation in PA patients (6,7). LVH itself is one of the most important predictors for major cardiac events and mortality and is associated with an increased risk of arrhythmia, MI and stroke (8).

In a recent study, we identified cortisol co-secretion as a key feature of PA (9) associated with an adverse metabolic risk phenotype, providing a logical explanation for important comorbidities observed in patients with primary aldosteronism more aligned with the effects of glucocorticoid rather than mineralocorticoid excess, such as insulin resistance and type 2 diabetes (10-13), and osteoporosis (14). Interestingly, pronounced LVH has also been described in patients with Cushing's syndrome (CS), who are also afflicted by arterial hypertension, impaired glucose tolerance and serum electrolyte imbalance (15,16). High cortisol levels in patients with CS are associated with an increased mortality rate due to cardiovascular complications (17).

Therefore, we hypothesized that cortisol co-secretion observed in PA might have additional adverse effects on cardiac function and cardiovascular outcome in PA patients. Thus, our aim was to investigate the impact of increased cortisol secretion on echocardiographic findings in patients with APA or BAH.

Methods

Patients

During 2008 and 2013 we consecutively enrolled 210 patients with primary aldosteronism at the Munich center of the German Conn's Registry. In 89 patients a urinary steroid metabolite excretion in 24-h urine was performed and of those 89, 73 patients with either APA (n=45) or BAH (n=28) had a technically accurate echocardiography examination, which represents the cohort included in this study. Analysis of urinary steroid metabolite excretion and echocardiography data represented post-hoc analyses. All patients gave written informed consent, and the protocol of the German Conn's registry was approved by the ethics committee of the University of Munich. At each visit, patients underwent standardized clinical phenotyping including collection of anthropometric data and clinical characteristics such as duration of hypertension and current medication.

The diagnostic procedures were performed according to the Endocrine Society Practice Guidelines (18,19). In short, PA was diagnosed by an elevated plasma aldosterone to renin ratio (ARR; cut-off 10.0 ng/mU, sitting position) and an abnormal confirmatory test (e.g. salt loading test, captopril challenge test). Antihypertensive medication was stopped (n=5) whenever possible prior to testing. Otherwise it was replaced by alpha 1-adrenergic receptor (doxazosin) or calcium-channel blockers (verapamil) (n=68). Subtype differentiation between unilateral and bilateral disease was based on adrenal vein sampling (AVS). In case of APA only patients who underwent ADX were included in the analysis. BAH patients were treated with MRA. In most patients, spironolactone was used at a dose of 25-50 mg per day. All patients were re-evaluated one year after treatment in a standardized fashion.

Laboratory analysis

Blood samples were drawn in a fasting state in sitting position at 8.00 a.m. Plasma aldosterone concentration was measured using the radioimmunoassay "aldosterone Coat-a-Count" (Biermann DPC). Active renin concentration was measured by the Liaison chemiluminescence assay (Diasorin). All other analyses were performed in our central laboratory using standard methods. To determine urinary steroid

excretion, the patients conducted a 24-hour urine collection. Subsequently, gas chromatography-mass spectrometry (GC-MS) in selected-ion-monitoring (SIM) analysis mode was performed to determine the urinary steroid metabolite excretion as described previously (9), allowing the quantification of 40 different steroid metabolites, including 3α,5β-tetrahydroaldosterone (THAldo), the major mineralocorticoid metabolite. Total glucocorticoid excretion was calculated as the sum of quantified metabolites of cortisol and cortisone, comprising tetrahydrocortisol, 5α-tetrahydrocortisol, tetrahydrocortisone, α- and β-cortol, α- and β-cortolone, 6β-hydroxycortisol, and urinary cortisol and cortisone (9).

Cardiac ultrasound examination

Comprehensive echocardiographic examination was conducted by experienced sonographers from the department of internal medicine I (cardiology) from the Ludwig-Maximilians-Universität München. The sonographers were blinded with regard to diagnosis and clinical details. Commercially available high-quality ultrasound systems were used (GE Healthcare Vivid 7, Philips iE 33). The patients were lying down in the left lateral decubitus position. Echocardiography included two-dimensional, M-Mode and Doppler ultrasound recordings. Images were obtained in the parasternal (long and short axis) and apical views. The left ventricular internal dimension (LVID), interventricular septum (IVS), posterior wall thickness (PWT) and left atrial dimension in diastole (LAd) were measured via parasternal long axis view. Echocardiographic parameters were measured according to the recommendation of the American Society of Echocardiography (20,21). Echocardiography-based left ventricular mass (LVM) estimation is generally calculated as the difference between epicardium delimited volume and left ventricular chamber volume multiplied by an estimate of myocardial density (22). The LVM was calculated by the Penn Convention formula: $LVM=1.04\ ([LVIDd+PWTd+IVSd]^3-[LVIDd]^3)-13.6g$ (23,24). Obesity is independently associated to LVH (25). Because of higher average values of BMI in our study cohort, LVH was determined as the left ventricular mass index (LVMI). LVM was indexed by $height^{2.7}$ to obtain LVMI. By using the LVMI we minimized the interference of obesity in LVM estimation (26). LVH was prospectively defined as a value of LVMI $\geq 50\ g/m^{2.7}$ in males and $\geq 47 g/m^{2.7}$ in females (27). Relative wall

thickness (RWT) was calculated according to the following equation: RWT=(IVSd + PWT)/LVIDd. LVH was separated in concentric hypertrophy with RWT ≥0.42 and eccentric hypertrophy with RWT <0.42 (21). Normal LVMI values and RWT values ≥0.42 were defined as concentric remodeling (28).

Statistical analysis

All values are expressed as median and 25th and 75th percentile if not mentioned otherwise. Within-group changes from baseline to follow-up were calculated by Wilcoxon signed-rank test. Spearman's Rank Order was used to perform bivariate correlation analysis. Stepwise multiple regression analysis was used for multivariate analysis. Two-tailed probability values of <5% were considered to be statistically significant. Statistical analysis was performed using standard statistical software (SPSS 23, IBM, Chicago, Illinois).

Results

Patient characteristics

Clinical characteristics of the total cohort of 73 patients with PA are shown in **Table 1**, the comparison of APA and BAH subgroups in **Table 2**. APA and BAH were diagnosed in 45 and 28 patients, respectively. As expected, at diagnosis, patients with APA had higher plasma aldosterone concentration (p=0.001), higher urinary THAldo concentrations (p=0.001) and lower potassium levels (p<0.001), and more pronounced renal impairment according to globular filtration rate (GFR; p=0.043). Total glucocorticoid excretion did not differ between groups (p=0.184).

Patient characteristics one year after initiation of treatment (MRA treatment in BAH, ADX in APA) are listed in **Tables 1+2**. Systolic and diastolic blood pressure and serum potassium levels normalized in both subgroups. As expected, defined daily doses (DDDs) of antihypertensive medication decreased significantly in the APA group, whereas in the BAH group there was only a trend towards lower DDDs. BMI remained stable in both groups and both groups had a decline in renal function. Triglyceride levels increased significantly in both groups, whereas HDL cholesterol levels decreased only in the BAH group (p=0.006). Pro-BNP, a potential indicator of cardiac preload, improved in both groups. The decline was not due to optimized treatment for heart failure. In fact, DDDs of ACE inhibitors/ angiotensin II receptor blockers (1.4 vs. 1.1; p=0.002), beta blockers (0.4 vs. 0.2; p=0.001) and diuretics (0.4 vs. 0.2; p<0.001) have decreased significantly at follow-up.

Echocardiographic findings in patients with unilateral aldosteronism and bilateral hyperplasia

Table 3 summarizes echocardiographic geometric characteristics in APA and BAH patients. LVMI was elevated, the IVS was thickened and the LA was enlarged in both groups at baseline. The overall prevalence of LVH was 85% before initiation of treatment, compared to 66% at follow-up. There was a shift from eccentric and concentric hypertrophy towards normal left ventricular geometry (**Suppl. Table 1**). As expected, LVMI improved in both APA (p<0.001) and BAH (p=0.024) patients with treatment (**Fig. 1**). The reduction of LVMI (ΔLVMI) was numerically greater in APA patients with a

significant decrease of LVIDd ($p<0.001$), PWTd ($p=0.020$) and IVSd ($p=0.001$). In BAH patients only LVIDd ($p=0.001$) improved significantly.

THAldo, total glucocorticoid excretion, urinary sodium excretion and left ventricular structure

As reported previously (9), both THAldo excretion and total glucocorticoid excretion were increased in PA patients (**Table 1**). In univariate analysis THAldo ($p=0.024$), urinary sodium excretion ($p=0.044$) and total glucocorticoid excretion ($p=0.018$) correlated with LVMI at time of diagnosis (**Suppl. Fig. 1+2**). In contrast, the relative changes in LVMI in response to treatment (ΔLVMI) correlated with total glucocorticoid excretion ($p=0.042$), but neither with THAldo ($p=0.776$) nor with urinary sodium excretion ($p=0.214$) (**Suppl. Fig. 1+2**). Moreover, when arbitrarily dividing PA patients into low and high steroid secretors, according to whether their THAldo and total glucocorticoid excretion was below or above the median, high total glucocorticoid excretion, but not THAldo, predicted a reduction in LVMI (**Fig. 2**). Similarly, in multivariate analyses, total glucocorticoid excretion and 24-h systolic blood pressure were strong predictors of left ventricular geometry changes, whereas THAldo did not have a significant effect in this model (**Table 4**). One year after treatment we could detect a significant decrease of total glucocorticoid excretion in APA patients. In accordance with our findings in APA patients with complete biochemical remission a higher decrease in total glucocorticoid excretion was followed by a more distinct reduction of LVMI at follow-up ($r^2=0.138$, $p=0.023$).

Discussion

This is the first study to evaluate the impact of glucocorticoid co-secretion on LVH in patients with PA. PA is characterized by increased aldosterone secretion, but in recent years a relevant cortisol co-secretion has been recognized in several case reports and small case series (29-32). We have recently reported that increased secretion of glucocorticoids is a major biochemical feature in a large proportion of patients with PA, whereas clinically overt signs of Cushing's syndrome are rare (9). We identified cortisol co-secretion in a substantial percentage of patients with APA and BAH and reported its association with parameters of the metabolic syndrome, such as BMI, HOMA-IR, and plasma lipids. Moreover, we found that after unilateral ADX glucocorticoid secretion normalized, followed by postoperative tertiary adrenal insufficiency in one third of patients. Based on this observation, we wondered whether total glucocorticoid excretion might also impact on the cardiac phenotype in PA.

Previous echocardiographic evaluations have already demonstrated excess LVM and more frequent LVH in patients with PA (5,33,34). Our patients with APA and BAH frequently had LVH according to LVMI; the most common left ventricular adaptation was eccentric hypertrophy. It has been described before, that high plasma aldosterone concentration results in eccentric changes in LV geometry (33,35) and that LVM is reduced by either MRA or ADX in patients with PA (36-39). A meta-analysis of four studies with an average follow-up of four years reported comparable effects for both treatment strategies (40). In line with this literature, our patients responded to treatment with a significant reduction in LVMI and an increase in the percentage of normal LV geometry.

At diagnosis, LVMI in the APA group was higher than in the BAH group. At follow-up, our APA patients showed a trend towards a more distinct reduction in LVMI compared to BAH patients without reaching statistical significance. Inhibition of MR-mediated aldosterone effects by specific medical treatment is an explanation for the comparable effects of MRA and ADX in LVM reduction. Our findings mirror previous studies reporting that the response of LVM reduction in adrenalectomized PA patients could occur earlier than in PA patients treated with MRA (36). Persistent hyperaldosteronemia with possible persistence of non-genomic effects of aldosterone has been proposed to potentially explain why

MRA treatment takes longer to show comparable effects than surgery (41). The results of our study suppose an impact of cortisol co-secretion on LVH and LV geometry. Total glucocorticoid excretion was positively correlated with baseline LVMI and ΔLVMI at follow-up. Therefore, patients with higher total glucocorticoid excretion showed higher decreases in LVMI after one year of treatment. In line with these findings, the decrease of glucocorticoid excretion correlated with the improvement of LVMI in our APA patients with biochemical remission.

Chronic cortisol hypersecretion, e. g. in patients with CS, is known to cause amongst others, truncal obesity, arterial hypertension, impaired glucose tolerance and dyslipidemia (42). However, also a variety of alterations in cardiac structure and function have been reported, including increased LVM, increased interventricular septum thickness and concentric hypertrophy or remodeling (15,16,43,44). CS is known to be associated with elevated cardiovascular morbidity and mortality (45). Cardiac dysfunction itself represents one of the most important cardiovascular complications affecting mortality. The two major forms of cardiac dysfunction in CS are cardiac hypertrophy and congestive heart failure (46,47). It is thought that the main cortisol effects leading to LVH are hypertension, potentiation of noradrenalin and angiotensin II responsiveness of the cardiomyocytes and cardiomyocyte proliferation and hypertrophy (48). MRs have similar affinity for aldosterone and cortisol. Glucocorticoid excess impairs conversion of cortisol to its MR-inactive cortisone by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSDS2) in classical aldosterone target issues as the distal nephron, leading to glucocorticoid-mediated mineralocorticoid effects (49,50). In the cardiomyocytes, 11β-HSDS2 is not expressed at relevant levels. Therefore, in physiologic circumstances the MR in cardiomyocytes is mostly occupied by cortisol, which circulates in much higher concentrations than aldosterone. In the event of cardiac tissue damage, cortisol acts as an MR agonist as shown by Mihailidou et al. in ischemia-reperfusion studies in rat heart Langendorff preparations (49). This effect can be blocked by spironolactone but not by the glucocorticoid/progesterone antagonist RU486. However, the abnormalities in LV structure and function have been reported to ameliorate (44) or even to be reversible upon normalisation of glucocorticoid excess (51).

Therefore, treatment with ADX or MRA should both be effective against the MR mediated effects of glucocorticoid excess on myocardial tissue. To our knowledge no glucocorticoid dependent MR-mediated effects on lipid and glucose metabolism have been reported so far. Therefore, MRA treatment could be inferior in this regard when increased glucocorticoid secretion in BAH remains unblocked during MRA treatment in glucocorticoid target organs, such as the endocrine pancreas, abdominal fat tissue and the liver. In the current study, however, the improvement of glucose metabolism following adrenalectomy was minimal, but a clinical relevant improvement in glucose homeostasis has been shown previously in several cohorts (52).

We acknowledge the limitation that steroid metabolite analysis and echocardiography were post hoc investigations and that our study was neither powered nor planned to examine differences between the two treatment strategies of PA, ADX and MRA treatment. However, following one year of MRA treatment, 54% of our BAH patients still had concentric remodeling or concentric hypertrophy as compared to 42% in APA patients. Therefore, this finding might be explained by ongoing glucocorticoid effects in BAH patients or inadequate MRA dosage. Unfortunately, we have only limited data for follow-up of urinary glucocorticoid excretion in BAH patients. In addition, one year of follow-up might be too short to detect full treatment effects of MRA treatment. Therefore, additional studies are required to address this issue.

It is known that patients with essential hypertension obtain LVM reduction by treatment with either ACE inhibitor or MRA and that a combination has an additive effect (53). Blood pressure levels and antihypertensive medication according to DDD´s were reduced in both groups one year after start of treatment. Although we detected comparable effects on 24-h blood pressure levels, the DDD´s showed numerically a greater reduction in adrenalectomized APA patients. A contributing factor can be the rather low dose of spironolactone of an average of 42 mg/d, in accordance with Endocrine Society Practice Guidelines which can be explained by clinical side effects including gynecomastia preventing further dose escalation. Similar to previous studies, most of the patients after ADX (58%) still needed antihypertensives because of residual hypertension (36,54).

The strengths of our study include the prospective standardized collection of all data and biomaterial within the context of the German Conn's registry, the homogeneously characterized study population, and the subtyping of all patients by adrenal vein sampling. A major limitation of the study is the very limited follow-up data for urinary steroid excretion (n=5) for BAH patients. Another limitation is the examination of left ventricular geometry by echocardiography. The main limitation of this technique is an inappropriate acoustic window, limiting patient inclusion to suitable candidates. Secondly, left ventricular parameters for estimation of LVM were generated by M-mode measurement. This is less accurate compared to real time three-dimensional echocardiography or 3D imaging by MRI (55). Thirdly, echocardiographic examinations in this study were performed by different experienced investigators, which could have had an influence on wall thicknesses estimation and therefore LVM and LVMI estimation. However, the investigators were blinded with regard to the underlying cause of disease, which we consider a strength of the study approach.

Conclusions

In this study, we investigated the effects of increased glucocorticoid secretion in 73 PA patients (45 APA, 28 BAH) on cardiac geometry. Our data show that total glucocorticoid excretion is associated with LVH independent of mineralocorticoid excess. Moreover, high total glucocorticoid excretion, but not THAldo predicted the ΔLVMI after adrenalectomy in APA patients. In summary, our data suggest a relevant role of glucocorticoid secretion in PA on LV geometry, pointing out the relevance of cortisol co-secretion in the context of PA.

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Table 1. Baseline and 1 year follow-up characteristics of all patients with primary aldosteronism.

Data are given as median and 25th and 75th percentile in square brackets. Asterisk indicates significance. Comparisons were performed by Wilcoxon signed rank test.

Patient characteristics (n=73)	**n**	**baseline**	**after treatment**	**p**
Gender [f/m]	73	28/45	--	n.c.
Age [years]	73	53 [43; 58]	--	n.c.
Duration of hypertension [months]	73	129 [52; 267]	--	n.c.
Antihypertensive agents [DDD]	73	3.0 [2.0; 4.3]	2.0 [0.1; 3.7]	0.002*
BMI [kg/m²]	73	27.7 [24.9; 30.9]	27.5 [24.9; 30.3]	0.705
Aldosterone [ng/l]	73	219.0 [148.0; 346.5]	124.5 [39.8; 198.8]	0.003*
Plasma renin [mU/l]	73	4.9 [2.2; 13.4]	18.9 [8.9; 44.6]	<0.001*
Serum potassium [mmol/l]	73	3.4 [3.0; 3.7]	4.2 [3.9; 4.5]0	<0.001*
Serum creatinine [mg/dl]	73	0.8 [0.7; 1.0]	1.0 [0.8; 1.2]	<0.001*
Serum urea [mg/dl]	73	13 [11; 16]	19 [15; 27]	<0.001*
GFR [ml/min/1.73 m²]	73	88.4 [72.3; 100.8]	73.9 [56.3; 85.9]	<0.001*
SBP [mmHg]	73	151 [138; 174]	133 [124; 142]	<0.001*
DBP [mmHg]	73	93 [86; 103]	87 [80; 93]	<0.001*
24h-SBP [mmHg]	57	144 [134; 157]	132 [125; 140]	<0.001*
24h-DBP [mmHg]	57	91 [84; 98]	84 [77; 88]	<0.001*
FPG [mg/dl]	73	102 [93; 113]	99 [91; 107]	0.033*
HDL-C [mg/dl]	70	56 [47; 70]	49 [40; 62]	<0.001*
LDL-C [mg/dl]	70	124 [92; 151]	126 [100; 142]	0.740
Triglycerides [mg/dl]	70	105 [72; 134]	114 [86; 178]	<0.001*
Total cholesterol [mg/dl]	70	197 [174; 227]	200 [174; 219]	0.995
Diabetes mellitus [n]	73	8 (11%)	8 (11%)	n.c.
Total glucocorticoid excretion [µg/24h]; median of healthy controls: 8262 [6380; 11044]	73	11807 [8270; 15266	--	n.c.
	44	12772 [9000; 16131]§	9458 [5578; 13460]§	<0.001*
Tetrahydroaldosterone excretion [µg/24h]; median of healthy controls: 30 [22; 44]	73	82 [52; 128]	--	n.c.
	44	88 [57; 131]§	21 [14; 39]§	<0.001*

Abbreviations: FPG: fasting plasma glucose; DDD: defined daily dose; SBP: systolic blood pressure; DBP: diastolic blood pressure; §: dataset of 44 patients with complete follow-up data, n.c.: not calculated.

Table 2. Baseline and 1 year follow-up characteristics of patients with primary aldosteronism according to subtype.

Data are given as median and 25th and 75th percentile in square brackets. Asterisk indicates significance. Comparisons were performed by Wilcoxon signed-rank-test and by McNemar-test. Differences between baseline values of both group were marked with # for p<0.05 and ## for p<0.0001.

Patient characteristics	**Aldosterone producing adenoma** (n=45)		**p**	**Bilateral adrenal hyperplasia** (n=28)		**p**
Time of assessment	**baseline**	**after ADX**		**baseline**	**after MRA**	
Age [years]	54 [46; 60]	--	n.c.	49 [41; 58]	--	n.c.
Sex [f/m]	17/28	--	n.c.	11/17	--	n.c.
Duration of hypertension [months]	130 [55; 250]	--	n.c.	130 [35; 283]	--	n.c.
BMI [kg/m²]	27.7 [24.9; 32.1]	28.1 [25.2; 30.3]	0.803	27.6 [25.0; 30.7]	27.1 [24.3; 30.4]	0.323
Aldosterone [ng/l]	242.0 [181.6; 427.9]	53.0 [35.0; 129.5]	<0.001*	159.5 [110.5;247.5]#	216.0 [160.0;388.6]	<0.001*
Plasma renin [mU/l]	5.5 [2.1; 12.1]	17.0 [9.1 45.1]	<0.001*	4.7 [2.5; 15.8]	19.9 [7.7; 45.0]	<0.001*
Serum potassium [mmol/l]	3.2 [2.8; 3.5]	4.2 [3.9; 4.5]	<0.001*	3.6 [3.2; 3.8]##	4.2 [3.9; 4.5]	<0.001*
Serum creatinine [mg/dl]	0.8 [0.8; 1.0]	1.1 [0.9; 1.3]	<0.001*	0.8 [0.7; 0.9]	0.8 [0.7; 1.1]	0.016*
Serum urea [mg/dl]	13 [11; 16]	22 [16; 29]	<0.001*	13 [10; 17]	16 [13; 24]	0.003*
GFR [ml/min/1.73 m²]	79.4 [69.9; 99.6]	68.8 [54.5; 77.8]	<0.001*	93.9 [84.1; 104.3]#	81.3 [71.5; 105.9]	0.031*
SBP [mmHg]	152 [139; 172]	133 [126; 144]	<0.001*	146 [134; 175]	132 [123; 137]	0.005*
DBP [mmHg]	93 [87; 105]	87 [80; 94]	0.001*	92 [86; 101]	88 [79; 93]	0.106
24-SBP [mmHg] †	149 [139; 157]	132 [125; 140]	<0.001*	144 [131; 155]	132 [123; 139]	0.032*
24-DBP [mmHg] †	91 [86; 99]	83 [77; 87]	<0.001*	91 [83; 98]	84 [76; 88]	0.007*
FPG [mg/dl]	102 [94; 112]	99 [91; 106]	0.043*	101 [91; 119]	100 [90; 112]	0.692
Diabetes mellitus [n]	5 (11%)	5 (11%)	n.c.	3 (11%)	3 (11%)	n.c.
HDL-C [mg/dl] †	54 [47; 69]	49 [42; 64]	0.076	56 [47; 72]	51 [39; 62]	0.006*
LDL-C [mg/dl] †	133 [92; 151]	126 [97; 145]	0.861	123 [92; 152]	126 [101; 142]	0.409
Triglycerides [mg/dl] †	103 [66; 134]	113 [79; 169]	0.001*	107 [80; 135]	117 [95; 190]	0.005*

Total cholesterol [mg/dl] †	203 [174; 231]	200 [170; 221]	0.480	192 [173; 221]	197 [175; 219]	0.402
Antihypertensive agents [DDD]	3.5 [2.0; 4.7]	1.5 [.0; 3.2]	<0.001*	3.0 [1.6; 3.5]	2.7 [1.0; 4.6]	0.848
Tetrahydroaldosterone excretion [µg/24h]	95 [63; 140]		n.c.	55 [40; 97]#		n.c.
	95 [62; 147]§	18 [13; 31]§	<0.001*	54 [39; 77]§§	60 [38; 70]§§	n.c.
Total glucocorticoid excretion [µg/24h]	12980 [9200; 15266]		n.c.	9908 [6328; 16109]		n.c.
	12563 [9015; 15516]§	9304 [5522; 11300]§	<0.001*	19943 [8573; 24897]§§	17073 [6603; 17581]§§	n.c.
Total sodium excretion [mmol/24h]	204 [136; 238]	164 [131; 257]	0.200	186 [150; 224]	196 [115; 240]	0.713
Pro-BNP[pg/ml]	117 [52; 297]	68 [32; 124]	<0.001*	96 [61; 167]	65 [41; 117]	0.023*

Abbreviations: ADX: adrenalectomy; MRA: mineralocorticoid receptor antagonist treatment; FPG: fasting plasma glucose; DDD: defined daily dose; SBP: systolic blood pressure; DBP: diastolic blood pressure; §: dataset of 44 patients with complete follow-up data, §§: dataset of 5 patients with complete follow-up data, n.c.: not calculated, †: Due to incomplete data the calculations for 24-SBP and 24-DBP (APA n=35, BAH n=22), and HDL-C, LDL-C, Triglycerides, Total cholesterol (APA n=43, BAH n=27) were performed with a reduced number of patients as listed in brackets.

Table 3. **Echocardiographic characteristics of patients with primary aldosteronism according to subtype.**

Data are given as median and 25th and 75th percentile in square brackets. Asterisk indicates significance. Comparisons were performed by Wilcoxon signed-rank-test.

Left ventricular parameters	**Aldosterone producing adenoma** (n=45)		**p**	**Bilateral adrenal hyperplasia** (n=28)		**p**
Time of assessment	**baseline**	**after ADX**		**baseline**	**after MRA**	
LVMI [g/m$^{2.7}$]	64.6 [54.7; 71.4]	56.5 [42.7; 63.6]	<0.001*	57.8 [50.3; 70.1]	53.5 [42.1; 65.2]	0.024*
ΔLVMI [g/m$^{2.7}$]		8.0 [1.5;18.3]	n.c.		6.4 [-2.0; 14.4]	n.c.
LVIDd [mm]	52 [49; 56]	50 [47; 53]	<0.001*	52 [47; 55]	49 [44; 53]	0.001*
LVIDs [mm]	31 [29; 36]	30 [27; 33]	0.128	31 [28; 34]	29 [26; 34]	0.083
PWTd [mm]	10 [9; 12]	10 [9; 11]	0.020*	10 [8; 11]	10 [9; 12]	0.319
IVSd [mm]	12 [11; 13]	11 [10; 13]	0.001*	12 [10; 13]	12 [10; 13]	0.072
RWTd [cm]	0.40 [0.35; 0.47]	0.40 [0.36; 0.46]	0.775	0.39 [0.33; 0.44]	0.43 [0.38; 0.50]	0.014*
LAd [mm]	42 [38; 46]	39 [36; 43]	<0.001*	42 [36; 47]	41 [33; 46]	0.090

Abbreviations: ADX: adrenalectomy; MRA: mineralocorticoid receptor antagonist treatment; LVMI: left ventricular mass indexed for height to the 2.7 power; ΔLVMI: reduction of left ventricular mass indexed for height to the 2.7 power after treatment; LVM: left ventricular mass, LVIDd: left ventricular internal dimension in diastole; LVIDs: left ventricular internal dimension in systole; PWTd: posterior wall thickness in diastole; IVSd: interventricular septum thickness in diastole; RWTd: relative wall thickness in diastole; LAd: left atrial internal dimension in diastole, n.c.: not calculated.

Table 4. Uni- and multivariate analyses of the associations with echocardiographic parameters in all patients with primary aldosteronism.

Data are given as p values. Asterisk indicates significance. Correlation analysis was performed using Spearman's Rank-Order test and stepwise multiple regression analysis.

	THAldo	**TGE**	**24h-SBP**	**THAldo, TGE, 24h-SBP**
Left ventricular parameters	**Univariate, p**	**Univariate, p**	**Univariate, p**	**Multivariate**
LVMI [$g/m^{2.7}$]	0.024*	0.018*	<0.001*	24h-SBP*
ΔLVMI [$g/m^{2.7}$]	0.776	0.042*	0.008*	24h-SBP*
LVIDd [mm]	0.531	0.003*	0.052	TGE*
IVSd [mm]	0.119	0.105	0.003*	24h-SBP*
PWTd [mm]	0.277	0.008*	0.003*	TGE*, 24h-SBP*
LAd [mm]	0.523	0.026*	0.008*	n.s.

Abbreviations: LVMI: left ventricular mass indexed for height to the 2.7 power; ΔLVMI: reduction of left ventricular mass indexed for height to the 2.7 power after treatment; LVM: left ventricular mass, LVIDd: left ventricular internal dimension in diastole; PWTd: posterior wall thickness in diastole; IVSd: interventricular septum thickness in diastole; LAd: left atrial internal dimension in diastole; 24h-SBP: 24-hour systolic blood pressure, THAldo: tetrahydroaldosterone; TGE: total glucocorticoid excretion; n.s.: no significant results.

Supplementary Table 1. Changes in left ventricular geometry of all patients with primary aldosteronism after one year of treatment.

Left ventricular geometry	**Aldosterone producing adenoma** (n=45)		**Bilateral adrenal hyperplasia** (n=28)	
Time of assessment	**baseline**	**after ADX**	**baseline**	**after MRA**
Normal (%)	13	22	18	25
Concentric Remodeling (%)	0	11	0	11
Eccentric Hypertrophy (%)	51	36	43	21
Concentric Hypertrophy (%)	36	31	39	43

Abbreviations: APA: unilateral disease; BAH: bilateral disease; ADX: adrenalectomy;
MRA: mineralocorticoid receptor antagonist treatment.

Figure Legends

Figure 1: **LVMI at baseline and after treatment in BAH and APA patients treated with either MRA or ADX.**

Median and 95 per cent confidence interval of LVMI are shown before (white bar) and after treatment (checkered bar). Asterisk indicates significance.

Abbreviations: APA: unilateral disease; BAH: bilateral disease; LVMI: left ventricular mass indexed for height to the 2.7 power.

Figure 2: **Reduction of LVMI following specific treatment according to baseline total glucocorticoid excretion and THAldo levels.**

Median and 95 per cent confidence interval of baseline glucocorticoid and THAldo excretion of PA patients with low and high total glucocorticoid (8390 µg/24h; 15266 µg/24h) or THAldo (52 µg/24h; 121 µg/24h) excretion are shown. Asterisk indicates significance.

Abbreviations: APA: unilateral disease; BAH: bilateral disease, LVMI: left ventricular mass indexed for height to the 2.7 power; TGE: total glucocorticoid excretion; THAldo: tetrahydroaldosterone.

Figure 1:

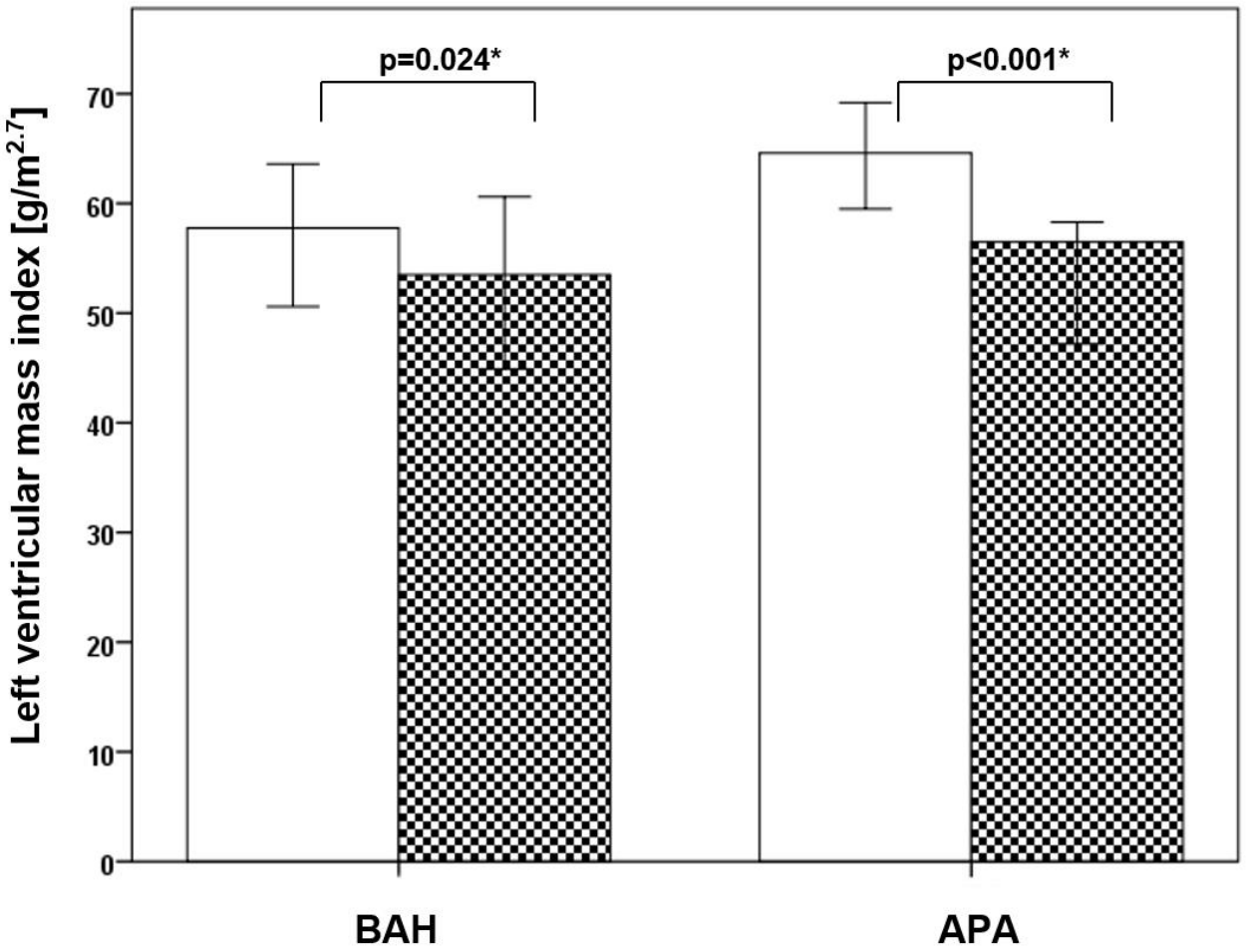
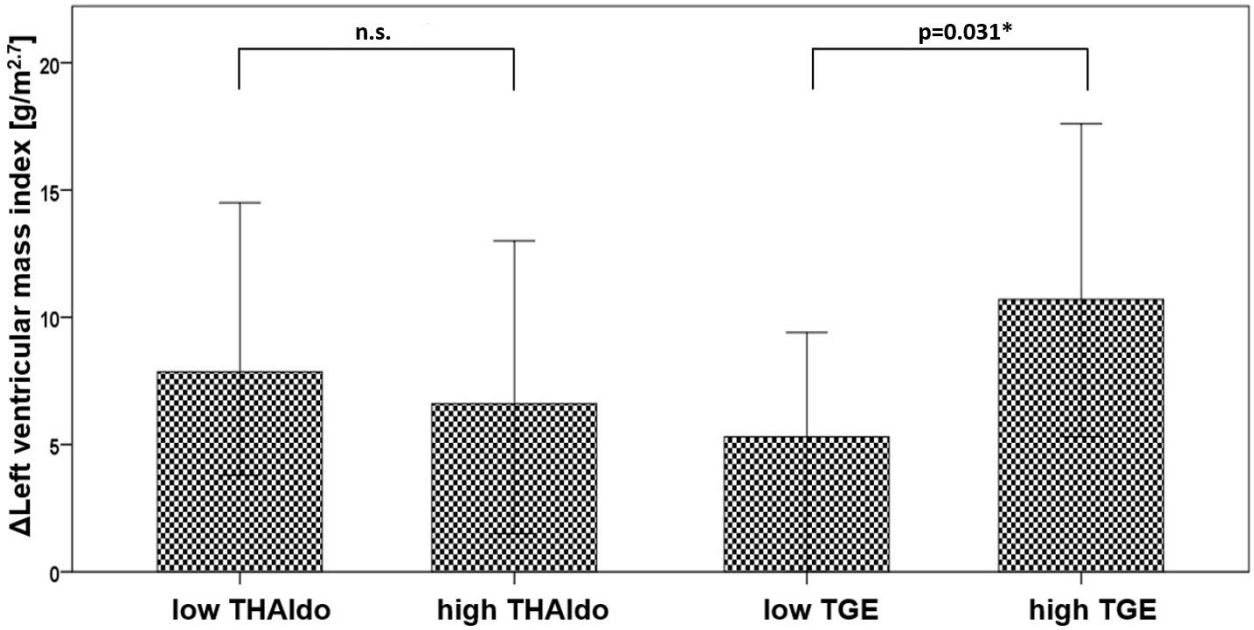

p=0.024*
p<0.001*
Left ventricular mass index [g/m2.7]
70
60
50
40
30
20
10
0
BAH
APA

Figure 2:


n.s.
p=0.031*
ΔLeft ventricular mass index [g/m2.7]
0
5
10
15
20
low THAldo
high THAldo
low TGE
high TGE

Supplementary Figure Legends

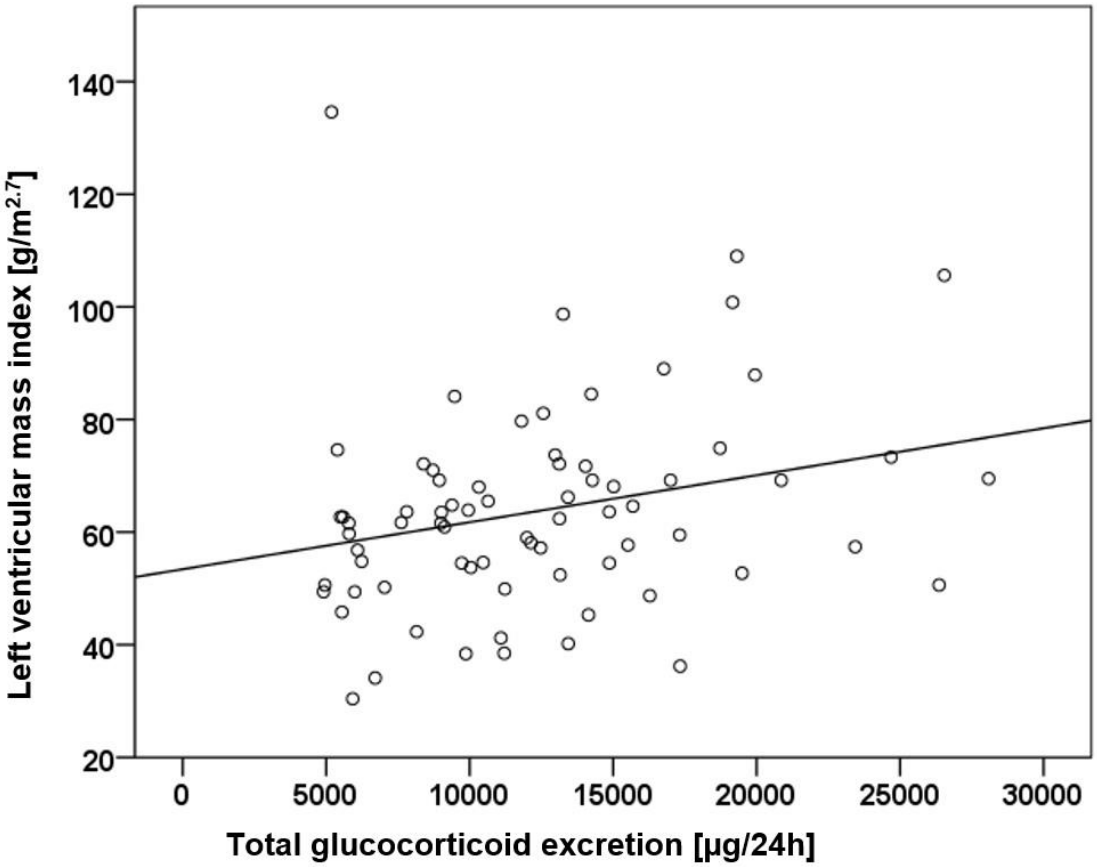
Supplementary Figure 1: Correlation of total glucocorticoid excretion with left ventricular mass indexed for height to the 2.7 power at baseline in patients with primary aldosteronism.

Supplementary Figure 2: Correlation of tetrahydroaldosterone excretion with left ventricular mass indexed for height to the 2.7 power at baseline in patients with primary aldosteronism.

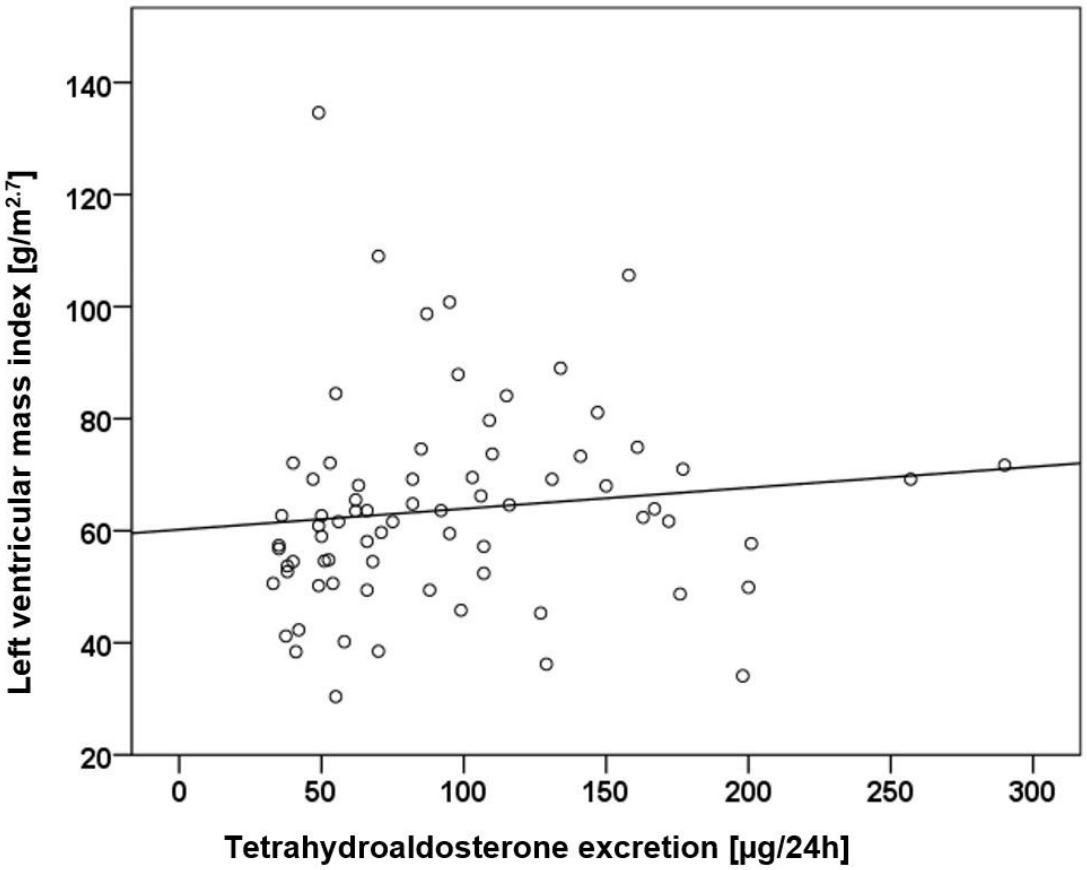
Supplementary Figure 3: Correlation of baseline glucocorticoid excretion with reduction of left ventricular mass indexed for height to the 2.7 power in patients with primary aldosteronism.

Supplementary Figure 4: Correlation of baseline tetrahydroaldosterone excretion with reduction of left ventricular mass indexed for height to the 2.7 power in patients with primary aldosteronism.

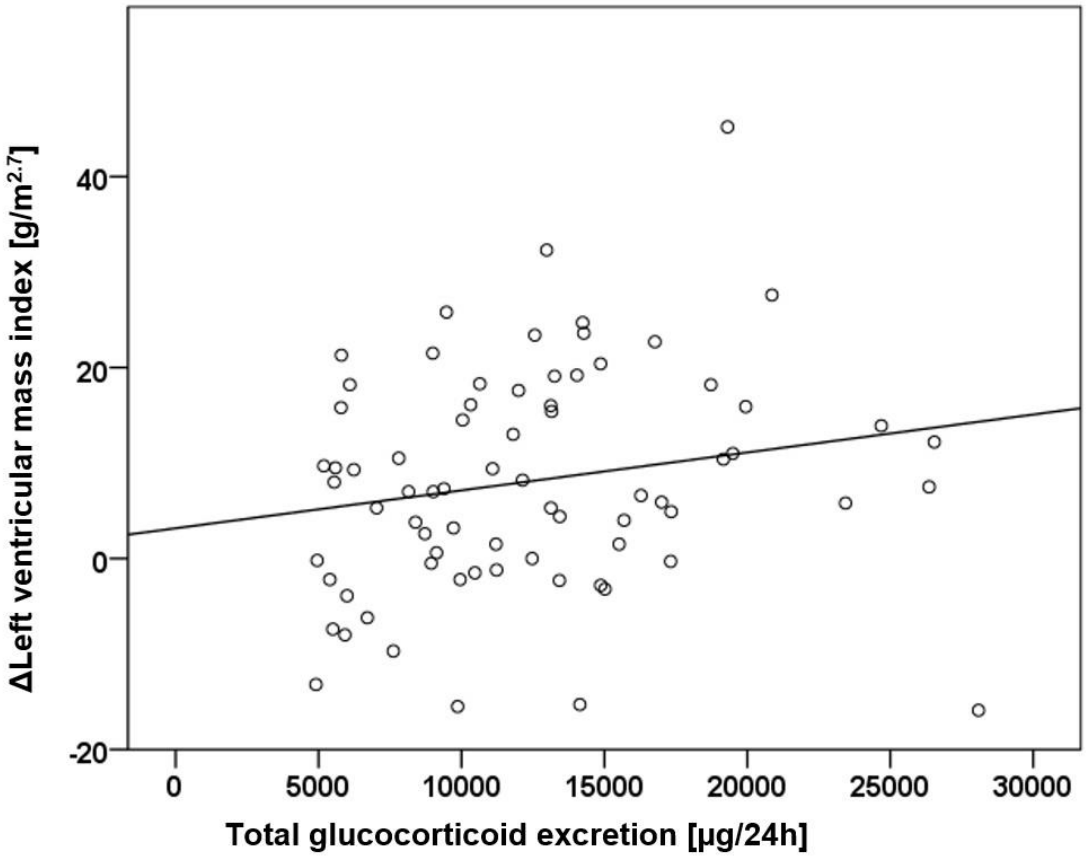
Supplementary Figure 1:



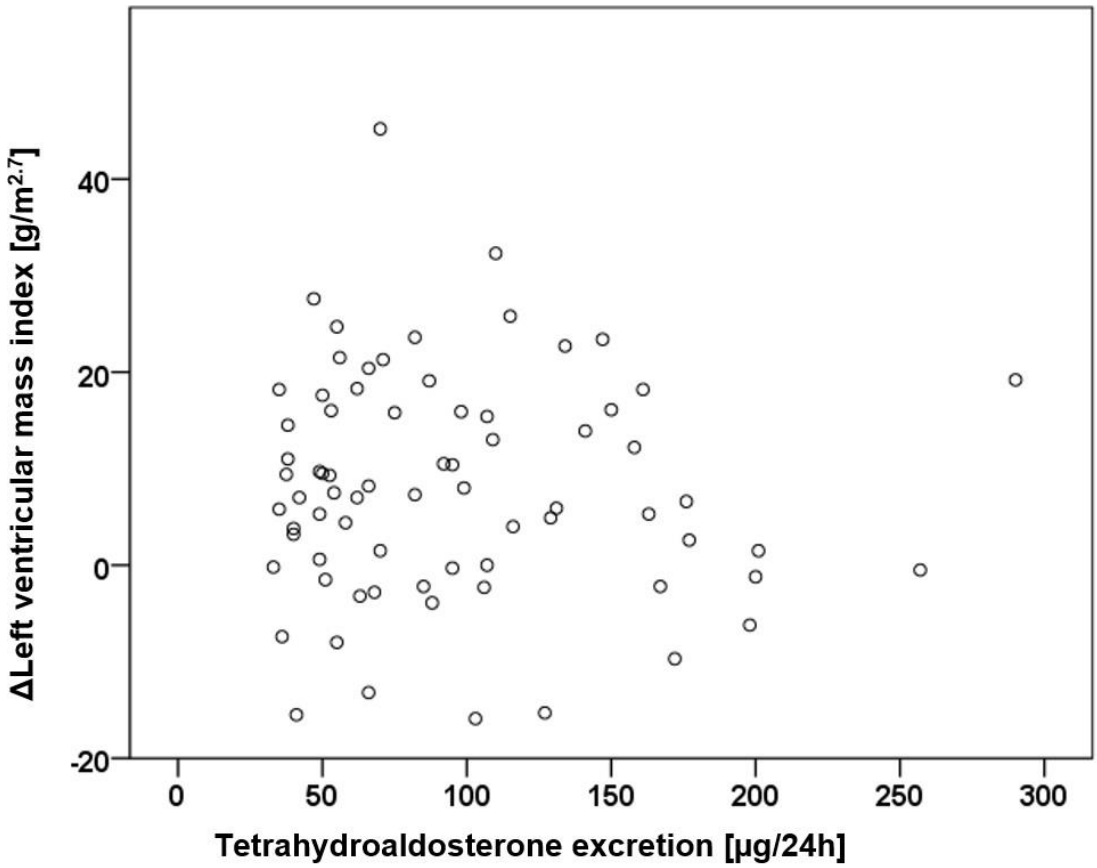
Supplementary Figure 2:



Supplementary Figure 3:



Supplementary Figure 4:



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